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Xin Xie

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EXAMINER

MUMMERT, STEPHANIE KANE

ART UNIT

PAPER NUMBER

1637

NOTIFICATION DATE

DELIVERY MODE

10/29/2010

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

EOfficeSD@mofo.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/538,443	<b>Applicant(s)</b> XIE ET AL.	
	<b>Examiner</b> STEPHANIE K. MUMMERT	<b>Art Unit</b> 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 27 May 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-3,6-13,18-25 and 28 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,6-13,18-25 and 28 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                        |                                                                   |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/27/10</u> .                                                 | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 27, 2010 has been entered.

Applicant's amendment filed on May 27, 2010 is acknowledged and has been entered. Claims 1 and 21 have been amended. Claims 4-5, 14-17, 26-27, 29-36 have been canceled. Claims 1-3, 6-13, 18-25, 28 are pending.

Claims 1-3, 6-13, 18-25, 28 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**This action is made NON-FINAL to address the new grounds of rejection.**

### **Previous Grounds of Rejection**

Applicant's argument regarding the correction of inventorship due to a typographical error is persuasive and inventorship has been corrected.

### **New Grounds of Rejection**

#### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on May 27, 2010 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said target cell or virus" in the final wherein clause following step d). It appears this limitation was not removed upon amendment to remove "or virus" language from the claims previously. There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 6-9, 12, 18, 20-25, 28 and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Dauer et al. (Biotechnology and Bioengineering, 1991, vol. 37, p. 1021-1028) in view of Inuma et al. (Int. J. Cancer, 2000, vol. 89, p. 337-344), Grevelding et al. (Nucleic Acids Research, 1996, 24(20), p. 4100-4101) and Wong et al. (US Patent 5,734,020; March 1998). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

With regard to claim 1, Dauer teaches a process for amplifying a nucleic acid of a target cell or virus, which process comprises:

- a) contacting a sample containing or suspected of containing a target cell or virus with a magnetic microbead (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1);
- b) allowing said target cell or virus, if present in said sample, to bind to said magnetic microbead nonspecifically or with low specificity to form a conjugate between said target cell or virus and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes, and where the pH is used to control binding to the particles and then

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release of the particles and where the contact is not mediated by a biomolecule and therefore is non-specific, see also Table 1);

c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said target cell or virus from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample).

With regard to claim 37, Dauer teaches a process for amplifying a nucleic acid of a cell, which process comprises:

- a) contacting a sample containing or suspected of containing a cell with a magnetic microbead (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1);
- b) allowing said cell, if present in said sample, to bind to said magnetic microbead nonspecifically or with low specificity to form a conjugate between said cell and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes, and where the pH is used to control binding to the particles and then release of the particles and where the contact is not mediated by a biomolecule and therefore is non-specific, see also Table 1); and
- c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said leukocyte cell from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample).

With regard to claim 6, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead comprises a magnetizable substance selected from the group consisting of a paramagnetic substance, a ferromagnetic substance and a ferrimagnetic substance (p. 1024, col. 2, where the magnetic microbead comprises a magnetic “seed” comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1).

With regard to claim 7, Dauer teaches an embodiment of claim 6, wherein the magnetizable substance comprises a metal composition (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic “seed” comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1).

With regard to claim 8, Dauer teaches an embodiment of claim 7, wherein the metal composition is a transition metal composition or an alloy thereof (p. 1024, col. 2, where the magnetic microbead comprises a magnetic “seed” comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1).

With regard to claim 9, Dauer teaches an embodiment of claim 8, wherein the transition metal is selected from the group consisting of iron, nickel, copper, cobalt, manganese, tantalum, zirconium and cobalt- tantalum-zirconium ( $\text{CoTaZr}$ ) alloy (p. 1024, col. 2, where the magnetic microbead comprises a magnetic “seed” comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1).

With regard to claim 18, Dauer teaches an embodiment of claim 1, which further comprises washing the separated conjugate to remove the undesirable constituents before applying separated conjugate to a nucleic acid amplification system (p. 1021, col. 2, where the cells are washed with water and air).

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With regard to claim 20, Dauer teaches an embodiment of claim 1, which is completed within a time ranging from about 0.5 minute to about 30 minutes (p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes).

With regard to claim 22, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a precipitation or centrifugation procedure (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 23, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a poisonous agent (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 24, Dauer teaches an embodiment of claim 1, which is conducted at an ambient temperature ranging from about 0°C to about 35°C without temperature control (p. 1025, col. 1, where the temperature is set at 25 +/- 2oC).

Regarding claims 1, 37 and 38, Dauer does not explicitly teach wherein the magnetic microbead is modified to comprise a hydroxyl, carboxyl or epoxy.

With regard to claim 1, Wong teaches wherein the magnetic microbead is modified to comprise a hydroxyl, carboxyl or an epoxy group (col. 2, lines 11-24, where the magnetic particle can be modified with a variety of functional groups including hydroxyl, carboxyl and epoxy groups).

With regard to claim 12, Wong teaches wherein the magnetic microbead is untreated or modified with an organic molecule (col. 2, lines 11-24, where the magnetic particle can be modified with a variety of functional groups including hydroxyl, carboxyl and epoxy groups).

Regarding claim 1 and 37, Dauer does not explicitly teach that the target cell is a leukocyte. Inuma teaches that leukocytes can be specifically targeted by magnetic beads comprising antibodies (p. 337, col. 2). Regarding claim 37, Dauer does not teach that the sample is obtained from whole blood.

With regard to claim 1, Inuma teaches a leukocyte target cell (p. 337, col. 2, where ‘anti-CD45 Mab-conjugated microbeads... bind to a common antigen of leukocytes’).

With regard to claim 37, Inuma teaches a) contacting a whole blood sample containing or suspected of containing a leukocyte cell with a magnetic microbead (p. 337, col. 2, where ‘anti-CD45 Mab-conjugated microbeads... bind to a common antigen of leukocytes’); and said leukocyte cells (p. 337, col. 2, where ‘anti-CD45 Mab-conjugated microbeads... bind to a common antigen of leukocytes’).

Regarding claim 1 and 37, Dauer does not explicitly teach that the cells can be applied to an amplification system.

With regard to claim 1 and 37, Grevelding teaches a method comprising d) applying said separated conjugate to a nucleic acid amplification system to amplify a nucleic acid from said target cell or virus, wherein said process does not comprise a step of lysing said target cell or virus to release said nucleic acid prior to applying said separated conjugate to said nucleic acid amplification system (Abstract, p. 4100, col. 1, where the technique of PCR is applied to whole organisms and has been applied to yeast and bacteria).

With regard to claim 2, Grevelding teaches an embodiment of claim 1, wherein the sample is a clinical sample comprising cells from the organism (p. 4100, col. 1, where the cells include *S. mansoni*, a blood fluke that infects humans).

With regard to claim 3, Grevelding teaches an embodiment of claim 1, wherein the sample is selected from the group consisting of serum, plasma, whole blood, sputum, cerebral spinal fluid, amniotic fluid, urine, gastrointestinal contents, hair, saliva, sweat, gum scrapings, marrow, tissue and cell culture (p. 4100, col. 1, where the cells include *S. mansoni*, a blood fluke that infects humans).

With regard to claim 21, Grevelding teaches an embodiment of claim 1, which is conducted in an eppendorf tube (p. 4100, where the process of setting up the reactions occurs in an eppendorf tube).

With regard to claim 25, Grevelding teaches an embodiment of claim 1, wherein the sample volume ranges from about 5 ul to about 50 ul (p. 4100, col. 2, where the reactions were carried out in a total volume of 25 ul).

With regard to claim 28, Grevelding teaches an embodiment of claim 1, wherein the nucleic acid amplification system is selected from the group consisting of polymerase chain reaction (PCR), ligase chain reaction (LCR), nucleic acid sequence-based amplification (NASBA), strand displacement amplification (SDA) and transcription-mediated amplification (TMA) (p. 4100, where the amplification was PCR; see legend to Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the target cells of Inuma using the method of separation taught by Dauer to arrive at the claimed invention with a reasonable expectation for success. As taught by Inuma, “prepared cells were resuspended in 80 µl of BSA-PBS mixed with 20 µl of CD45 microbeads for 15 min at 4°C and passed down the MACS column” (p. 338, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been

motivated to have analyzed the target cells of Inuma using the method of separation taught by Dauer to arrive at the claimed invention with a reasonable expectation for success.

It also would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Dauer and Inuma to include the additional functional groups of Wong to arrive at the claimed invention with a reasonable expectation for success. As taught by Wong, "This invention also includes porous inorganic magnetic materials, preferably siliceous materials, surface modified to provide functional groups such as amino, hydroxyl, carboxyl, epoxy, aldehyde, sulfhydryl, phenyl or long chain alkyl groups to facilitate the chemical and/or physical attachment of biological molecules and other moieties, e.g., enzymes, antibodies, oligopeptides, oligonucleotides, oligosaccharides or cells. Surface modification to create such functionality may be accomplished by coating with organic silanes. See, e.g., Bonded Stationary Phases in Chromatography, ed. by E. Grushka (1974). Alternate methods for providing derivatized or functional group containing surfaces on the magnetic products of this invention include U.S. Pat. Nos. 3,983,299 and 4,554,088." (col. 2, lines 11-24). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Dauer and Inuma to include the additional functional groups of Wong to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success. As taught by Grevelding,

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“recently protocols were introduced that allow PCR amplification without DNA extraction” and “we show that PCR amplification is possible from whole, undissected larvae and adults of the fruitfly *Drosophila melanogaster* and the blood fluke, *Schistosoma mansoni* without preceding DNA isolation.” Regarding the applicability of the method to other types of cells, Grevelding teaches “Since it worked both with an organism covered by a tegument as well as one surrounded by a chitinous cuticle, it is expected that it should also be applicable for a variety of other eukaryotic organisms” (p. 4101, col. 1). While Grevelding teaches isolation from whole organisms, the technique of amplification directly from cells without prior DNA extraction is clearly supported by the teachings of Grevelding. Therefore, one of ordinary skill in the art would have been motivated to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success.

Claims 5 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dauer in view of Inuma and Grevelding and Wong as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 above, and further in view of Lopez-Sabater et al. (Letters in Applied Microbiology, 1997, vol. 24, p. 101-104). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Dauer in view of Inuma and Grevelding and Wong teaches all of the limitations of claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 as recited in the 103 rejection stated above.

However, Dauer does not teach removing cells suspected of containing a virus before contacting

the sample with microbeads. Lopez-Sabater teaches a method for the magnetic immunoseparation for detection of viral sequences by PCR (Abstract).

With regard to claim 5, Lopez-Sabater teaches an embodiment of claim 1, wherein the target virus is an eucaryotic cell virus or a bacteriophage (p. 102, col. 1, where the cells were inoculated with virus and the cells are eucaryotic and therefore the target virus is a eucaryotic cell virus).

With regard to claim 29, Lopez-Sabater teaches an embodiment of claim 1, which further comprises removing cells from a sample containing or suspected of containing a target virus or bacteriophage before contacting the sample with a magnetic microbead (p. 102, col. 1, 'recovery' heading, where the oyster cells were diced and homogenized, therefore the cells were removed before contacting with a magnetic microbead).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the technique of homogenization of a sample suspected of containing a virus as taught by Lopez-Sabater to the method of isolation and analysis taught by Dauer to arrive at the claimed invention with a reasonable expectation for success. As taught by Lopez-Sabater, "samples (20g) of shucked American oyster... were inoculated with levels of HAV ranging from 10 to 10<sup>3</sup> pfu" and "after 1 hour at room temperature, artificially contaminated oysters were diced with sterile scissors" and subsequently homogenized (p. 102, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the technique of homogenization of a sample suspected of containing a virus as taught by Lopez-Sabater to the method of isolation and analysis taught by Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

Claim 10 is rejected under 35 U.S.C. 103(a) as being obvious over Dauer in view of Inuma and Grevelding and Wong as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 and further in view of Ughelstad et al. (WO83/03920; November 1983). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Regarding magnetic beads, Dauer teaches that the magnetic particles are ferromagnetic. Ughelstad teaches the details of the process of forming magnetic particles (Abstract).

With regard to claim 10, Ughelstad teaches an embodiment of claim 7, wherein the metal composition is Fe<sub>3</sub>O<sub>4</sub> (p. 9, where the metal comprises Fe<sub>3</sub>O<sub>4</sub>).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the specific teachings of Ughelstad to the particles of Dauer to arrive at the claimed invention with a reasonable expectation for success. As taught by Dauer, “The magnetic seed is a ferromagnetic  $\gamma$ -iron oxide ( $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>) or maghemite” (p. 1024, col. 2). Ughelstad teaches wherein the method composition comprises Fe<sub>3</sub>O<sub>4</sub> specifically (see p. 9). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the specific teachings of Ughelstad to the particles of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

Claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 38 are rejected under 35 U.S.C. 103(a) as being obvious over Dauer et al. (Biotechnology and Bioengineering, 1991, vol. 37, p. 1021-1028) in view of O'Neill et al. (US Patent 6,187,546; February 2001) and Grevelding et al. (Nucleic Acids

Research, 1996, 24(20), p. 4100-4101) and Wong et al. (US Patent 5,734,020; March 1998).

Dauer teaches a method of isolating cells using magnetic particles (Abstract).

With regard to claim 1, Dauer teaches a process for amplifying a nucleic acid of a target cell or virus, which process comprises:

- a) contacting a sample containing or suspected of containing a target cell or virus with a magnetic microbead not comprising a biomolecule that binds to said target cell or virus with high specificity (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1);
- b) allowing said target cell or virus, if present in said sample, to bind to said magnetic microbead to form a conjugate between said target cell or virus and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes, and where the pH is used to control binding to the particles and then release of the particles);
- c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said target cell or virus from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample), wherein said biomolecule is selected from the group consisting of an antibody, an amino acid, a peptide, a protein, a nucleoside, a nucleotide, an oligonucleotide, a nucleic acid, a vitamin, a monosaccharide, an oligosaccharide, a carbohydrate, a lipid and a complex thereof (Table 1, p. 1024, col. 2, where the magnetic particle is not coated with a biomolecule or other affinity group).

With regard to claim 38, Dauer teaches a process for amplifying a nucleic acid of an epithelial cell, which process comprises:

- a) contacting a sample containing or suspected of containing a cell with a magnetic microbead (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1);
- b) allowing said cell, if present in said sample, to bind to said magnetic microbead nonspecifically or with low specificity to form a conjugate between said cell and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes, and where the pH is used to control binding to the particles and then release of the particles); and
- c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said cell from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample).

With regard to claim 6, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead comprises a magnetizable substance selected from the group consisting of a paramagnetic substance, a ferromagnetic substance and a ferrimagnetic substance (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1).

With regard to claim 7, Dauer teaches an embodiment of claim 6, wherein the magnetizable substance comprises a metal composition (p. 1024, col. 2, where baker's yeast were

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the target cells and where the magnetic microbead comprises a magnetic “seed” comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1).

With regard to claim 8, Dauer teaches an embodiment of claim 7, wherein the metal composition is a transition metal composition or an alloy thereof (p. 1024, col. 2, where the magnetic microbead comprises a magnetic “seed” comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1).

With regard to claim 9, Dauer teaches an embodiment of claim 8, wherein the transition metal is selected from the group consisting of iron, nickel, copper, cobalt, manganese, tantalum, zirconium and cobalt- tantalum-zirconium (CoTaZr) alloy (p. 1024, col. 2, where the magnetic microbead comprises a magnetic “seed” comprising ferromagnetic gamma-iron oxide or maghemite ( $\text{Fe}_2\text{O}_3$ ); see Table 1).

With regard to claim 12-13, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead is untreated or modified with an organic molecule such as hydroxyl, carboxyl or epoxy (Table 1, p. 1024, col. 2, where the magnetic particle is not coated with a biomolecule or other affinity group).

With regard to claim 18, Dauer teaches an embodiment of claim 1, which further comprises washing the separated conjugate to remove the undesirable constituents before applying separated conjugate to a nucleic acid amplification system (p. 1021, col. 2, where the cells are washed with water and air).

With regard to claim 20, Dauer teaches an embodiment of claim 1, which is completed within a time ranging from about 0.5 minute to about 30 minutes (p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes).

With regard to claim 22, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a precipitation or centrifugation procedure (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 23, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a poisonous agent (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 24, Dauer teaches an embodiment of claim 1, which is conducted at an ambient temperature ranging from about 0°C to about 35°C without temperature control (p. 1025, col. 1, where the temperature is set at 25 +/- 2oC).

Regarding claims 1, 37 and 38, Dauer does not explicitly teach wherein the magnetic microbead is modified to comprise a hydroxyl, carboxyl or epoxy.

With regard to claim 1, Wong teaches wherein the magnetic microbead is modified to comprise a hydroxyl, carboxyl or an epoxy group (col. 2, lines 11-24, where the magnetic particle can be modified with a variety of functional groups including hydroxyl, carboxyl and epoxy groups).

With regard to claim 12, Wong teaches wherein the magnetic microbead is untreated or modified with an organic molecule (col. 2, lines 11-24, where the magnetic particle can be modified with a variety of functional groups including hydroxyl, carboxyl and epoxy groups).

Regarding claim 38, Dauer does not explicitly state that the sample comprises saliva or that the target cell comprises an epithelial cell. O'Neill teaches analysis of epithelial cells in saliva samples (Abstract).

With regard to claim 38, O'Neill teaches a saliva sample containing or suspected of containing an epithelial cell (col. 20, where epithelial cells are exfoliated into saliva or sputum), wherein the epithelial cell is enriched and isolated by binding to a magnetic particle (col. 20, lines 32-35, where epithelial cells are enriched using magnetic particle sorting).

Regarding claims 1 and 38, neither Dauer or O'Neill explicitly teach that the cells can be applied to an amplification system.

With regard to claim 1, Grevelding teaches a method comprising d) applying said separated conjugate to a nucleic acid amplification system to amplify a nucleic acid from said target cell or virus, wherein said process does not comprise a step of lysing said target cell or virus to release said nucleic acid prior to applying said separated conjugate to said nucleic acid amplification system (Abstract, p. 4100, col. 1, where the technique of PCR is applied to whole organisms and has been applied to yeast and bacteria).

With regard to claim 38, Grevelding teaches a method comprising d) applying said separated conjugate to a nucleic acid amplification system to amplify a nucleic acid from said target cell or virus (Abstract, p. 4100, col. 1, where the technique of PCR is applied to whole organisms and has been applied to yeast and bacteria).

With regard to claim 2, Grevelding teaches an embodiment of claim 1, wherein the sample is a clinical sample comprising cells from the organism (p. 4100, col. 1, where the cells include *S. mansoni*, a blood fluke that infects humans).

With regard to claim 3, Grevelding teaches an embodiment of claim 1, wherein the sample is selected from the group consisting of serum, plasma, whole blood, sputum, cerebral spinal fluid, amniotic fluid, urine, gastrointestinal contents, hair, saliva, sweat, gum scrapings,

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marrow, tissue and cell culture (p. 4100, col. 1, where the cells include *S. mansoni*, a blood fluke that infects humans).

With regard to claim 21, Grevelding teaches an embodiment of claim 1, which is conducted in an eppendorf tube (p. 4100, where the process of setting up the reactions occurs in an eppendorf tube).

With regard to claim 25, Grevelding teaches an embodiment of claim 1, wherein the sample volume ranges from about 5 ul to about 50 ul (p. 4100, col. 2, where the reactions were carried out in a total volume of 25 ul).

With regard to claim 28, Grevelding teaches an embodiment of claim 1, wherein the nucleic acid amplification system is selected from the group consisting of polymerase chain reaction (PCR), ligase chain reaction (LCR), nucleic acid sequence-based amplification (NASBA), strand displacement amplification (SDA) and transcription-mediated amplification (TMA) (p. 4100, where the amplification was PCR; see legend to Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success. As taught by Grevelding, “recently protocols were introduced that allow PCR amplification without DNA extraction” and “we show that PCR amplification is possible from whole, undissected larvae and adults of the fruitfly *Drosophila melanogaster* and the blood fluke, *Schistosoma mansoni* without preceding DNA isolation.” Regarding the applicability of the method to other types of cells, Grevelding teaches “Since it worked both with an organism covered by a tegument as well as one surrounded by a

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chitinous cuticle, it is expected that it should also be applicable for a variety of other eukaryotic organisms” (p. 4101, col. 1). While Grevelding teaches isolation from whole organisms, the technique of amplification directly from cells without prior DNA extraction is clearly supported by the teachings of Grevelding. Therefore, one of ordinary skill in the art would have been motivated to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success.

It also would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Dauer and Grevelding to include the additional functional groups of Wong to arrive at the claimed invention with a reasonable expectation for success. As taught by Wong, “This invention also includes porous inorganic magnetic materials, preferably siliceous materials, surface modified to provide functional groups such as amino, hydroxyl, carboxyl, epoxy, aldehyde, sulfhydryl, phenyl or long chain alkyl groups to facilitate the chemical and/or physical attachment of biological molecules and other moieties, e.g., enzymes, antibodies, oligopeptides, oligonucleotides, oligosaccharides or cells. Surface modification to create such functionality may be accomplished by coating with organic silanes. See, e.g., Bonded Stationary Phases in Chromatography, ed. by E. Grushka (1974). Alternate methods for providing derivatized or functional group containing surfaces on the magnetic products of this invention include U.S. Pat. Nos. 3,983,299 and 4,554,088.” (col. 2, lines 11-24). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Dauer and Grevelding to include the

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additional functional groups of Wong to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Dauer and Grevelding to the analysis and separation of epithelial cells in saliva as taught by O'Neill to arrive at the claimed invention with a reasonable expectation for success. O'Neill teaches, "Exfoliated cells in sputum or saliva or selectively separated" and "iii) After ensuring that the saliva or sputum is diluted enough to reduce its viscosity, immunomagnetic Ber-EP4 beads, of suspension are added to the diluted saliva or sputum and clean-up is performed as for urine" (col. 20, lines 3-5). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Dauer and Grevelding to the analysis and separation of epithelial cells in saliva as taught by O'Neill to arrive at the claimed invention with a reasonable expectation for success.

Claims 11 and 19 are rejected under 35 U.S.C. 103(a) as being obvious over Dauer in view of O'Neill and Grevelding and Wong as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 38 and further in view of Dzieglewska (WO98/51693). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Regarding claims 11 and 19, Dauer does not teach these specific details regarding the elements of the method as claimed.

With regard to claim 11, Dzieglewska teaches an embodiment of claim 1, wherein the magnetic microbead has a diameter ranging from about 5 to about 50,000 nanometers (p. 9, lines 26-33, where the bead has a diameter of 1-2  $\mu\text{m}$ ).

With regard to claim 19, Dzieglewska teaches an embodiment of claim 1, which is automated (p. 16, lines 12-14, where the method can be amenable to automation).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Dauer to the include elements of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success. As taught by Dzieglewska, "Representative samples thus include whole blood and blood-derived products such as plasma or buffy coat, urine, faeces, cerebrospinal fluid or any other body fluids, tissues, cell cultures, cell suspensions etc., and also environmental samples such as soil, water, or food samples" (p. 5). Dzieglewska also teaches "The invention is advantageously amenable to automation, particularly if particles, and especially, magnetic particles are used as the support" (p. 16). While Dzieglewska teaches a method that comprises lysis of cells prior to amplification, the elements of the claims represented by Dzieglewska are obvious in combination with the teaching of Dauer and Greveling. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Dauer and Greveling to the include elements of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

### ***Response to Arguments***

Applicant's arguments with respect to claims 1-13 and 18-29 have been considered but are moot in view of the new ground(s) of rejection.

However, insofar as Applicant's arguments apply to the instantly amended claims, the arguments will be considered. First of all, Applicant indicates that the inventorship of the application needs to be corrected to reflect the correct name, Jing Cheng. The instant inventorship, prior to correction, states Jing Chen.

Applicant's arguments are persuasive and the inventorship has been corrected.

Next, Applicant traverses the rejection of claims as being obvious over Dauer in view of Grevelding and Inuma (or O'Neill). Applicant argues "neither Inuma nor O'Neill teaches or even suggests non-specific or low-specificity magnetic separation of mammalian cells, particularly leukocytes or epithelial cells" (p. 11 of remarks). Applicant goes on to argue at length regarding separation of mammalian cells (p. 11 of remarks). Applicant discusses the features of the invention. Applicant argues that the "entire line of reasoning is scientifically flawed" and argues that "the prior art taught away from magnetic beads that bind to cells non-specifically" and cites a passage in Safarik reference (p. 13 of remarks). Applicant goes on to argue that the rejection is ignoring structural differences between yeast and mammalian cells, and points to the thick cell wall in yeast as compared to leukocytes that do not have a cell wall and that the chemical composition of the yeast cells have a different composition (p. 14 of remarks).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., mammalian

cells) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Next, it is noted that while Applicant's arguments regarding the differences between yeast cells and epithelial cells, and regarding an apparent teaching away in the art, these arguments are also not persuasive. Applicant appears to be arguing inoperability of the combination of references. However, while the differences between yeast and epithelial cells may be significant, Applicant successfully uses magnetic microparticle beads in separation of these cells that are structurally indistinguishable from the magnetic seed particles taught by Dauer. Therefore, an argument that magnetic particles as claimed would be unsuccessful in capture of epithelial or leukocyte cells due to a particular feature of the cell membrane raises issues of the operability of the instant invention. In the absence of a feature which clearly renders the magnetic particles of Dauer distinct from those instantly claimed, it is not clear how the beads would function properly in the instantly claimed invention but would have no expectation for success when applied to the same cell types. Clarification of this position, in light of this argument, is requested.

Next, it is noted that the claims, as amended, include surface modifications which, as argued by Wong, can "facilitate the chemical and/or physical attachment of biological molecules and other moieties, e.g., enzymes, antibodies, oligopeptides, oligonucleotides, oligosaccharides or cells". Therefore, in light of this teaching, one of skill, just considering the teachings of Dauer and Wong would have a reasonable expectation that the magnetic particles could be useful for separation of a variety of cell types, including epithelial and leukocyte cells as claimed.

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References such as Iinuma and O'Neill, merely teach that magnetic isolation (though mediated specifically by antibody labeling) can and has been used for separation of the claimed cell types. One of ordinary skill in the art would also recognize that while the references teach away from non-specific binding when the beads are labeled with a specific binding moiety, like an antibody, this teaching is clearly not teaching away from any use of the beads to non-specifically bind or label cells as suggested by Dauer and Wong. Therefore, Applicant's arguments are not persuasive and the rejections are maintained.

Applicant traverses the rejection of claims as being obvious over Dauer, Grevelding and Ughelstad or in view of Dzieglewska.

Regarding Ughelstad or Dzieglewska, Applicant fundamentally argues that either Ughelstad or Dzieglewska do not cure the deficiencies of the primary references. These arguments are not persuasive for the reasons stated above. The rejections are maintained.

### ***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hardingham et al. (Cancer Research, 1993, vol. 53, p. 3455-3458) teaches a general method for immunobead isolation of circulating tumor cells followed by PCR (Abstract).

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Stephanie K. Mummert/  
Primary Examiner, Art Unit 1637